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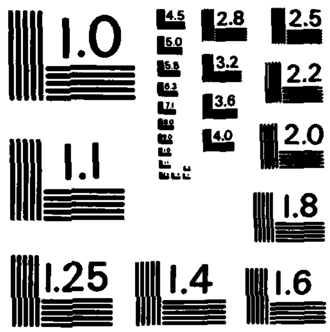

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In a second experiment right hemisphere AEFs and AEPs in response to contralateral ear stimulation tone in these 12 subjects were combined with similar previous data from 24 subjects, providing a total of 36 subjects, to examine the comparability of the AEP P50 waveform and the AEF P50 analog. The latency of the P50 was found to decrease as a function of increasing stimulus intensity for both AEFs and AEPs but the P50 latency was consistently shorter in magnetic compared to potential recordings.

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Auditory evoked magnetic fields: A replication, with comments on the magnetic P50 analog*

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Recent studies have demonstrated substantial differences between auditory evoked magnetic fields (AEFs) recorded from regions overlying the auditory cortex and EEG auditory evoked potentials (AEPs) recorded from the same location and in response to the same stimuli. AEFs exhibit more pronounced interhemispheric asymmetry, being of higher amplitude in response to contralateral than to ipsilateral ear stimulation (1,2). When the auditory stimuli consisted of 100 msec long 1 KHz tone pips, 100 msec long equal sound pressure level (SPL) white noise bursts, or equal SPL clicks, AEFs were of highest amplitude in response to tones, of intermediate amplitude in response to white noise, and of lowest amplitude in response to clicks. Simultaneously recorded AEPs did not vary similarly with stimulus type. This variation of AEF amplitude as a function of stimulus type parallels previously reported auditory cortex unit activation by similar stimuli, suggesting AEFs may be more closely reflecting cortical unit activity patterns, whereas other influences may be influencing AEP amplitude (3).

In a recent study recording from right hemisphere auditory cortical regions, AEF amplitude to 100 msec long tone pips delivered at 40, 60, 80 and 100 dB sound pressure level (SPL)*, was shown to increase rapidly at 40 and 60 dB stimulus SPL intensity, but then plateau or even decrease slightly at higher stimulus intensities. EEG AEPs recorded from the same location exhibited a linear increase in response amplitude with increasing stimulus intensity. These findings were interpreted as suggesting that the AEFs may be reflecting local intraneuronal currents in auditory cortical regions, whereas AEPs may be reflecting more widespread extracellular currents, including nonspecific thalamacortical influences (4).

The present study was designed to serve 2 functions, first, to independently replicate the previously reported findings on interhemispheric AEF asymmetry and the nature of the AEF amplitude intensity function, and secondly, to provide additional data about the configuration and latency of the magnetic analog of the AEP P50 wave recorded from the scalp overlying auditory cortical regions.

Methods

There were 2 experiments in this study. Experiment 1, an independent replication of previously described interhemispheric asymmetry and field amplitude vs. stimulus intensity functions, involved recording 12 subjects using an experimental paradigm similar to those used previously to evaluate these issues. Experiment 2, which concerned examining the magnetic analog of the EEG AEP P50 waveform, involved merging certain data from the above mentioned 12 subjects and previously recorded data from 24 subjects, so that summary data would be available for 36 subjects. Three of the 12 subjects studied in the present experiment also participated in the earlier 24 subject response amplitude-stimulus intensity experiment.

Experiment 1

We recorded AEFs and AEPs from both hemispheres of 12 normal adult subjects, six male and six female. Recordings were made over a point 1/4 of the distance from T_4 to C_4, or T_3 to C_3. Subjects were recorded sitting in a contoured foam padded chair located inside a 2.4 x 2.4 x 2.5 m room constructed of 4 cm thick seam welded aluminum panels. The magnetic sensor was a figure-eight SQUID gradiometer with a 4 cm baseline oriented so as to be maximally sensitive to a current dipole oriented normal to the Sylvian fissure. The SQUID itself was the field detector, and no flux transformer was necessary. The gradiometer measured the transverse gradient of the magnetic

* reference SPL = .0002 dynes cm^2

field component normal to the scalp, that is, dBz/dy, where Bz is the magnetic field perpendicular to the scalp, and y is the distance measured parallel to the surface of the scalp. A figure 8 gradiometer gives maximum output when directly over and oriented with the appropriate axis parallel to an active current dipole (see reference (5) for details). Conventional gold cup EEG electrodes were placed over the recording sites and were referenced to the opposite ear lobe.

Stimuli consisted of aperiodic 100 msec duration 1 KHz tone bursts with a modal interstimulus interval of approximately 700 msec. A constantly running sine wave generator was gated to an audio amplifier. Tones were led from the speaker to the subjects by a system of plastic tubing. There was no appreciable rise time for the tone stimuli, and phase at stimulus onset was random. Sound transit time from speaker to subject was 23 msec. Stimuli were presented at 4 sound pressure levels, 40, 60, 80 and 100 dB as measured at the ear with a sound pressure level meter. EEG and MEG signals were amplified, filtered from 2-40 Hz, and time averaged on a dual channel signal averager for 500 msec following each of 128 stimulus presentations. Recordings were made over each hemisphere in response to both contralateral and ipsilateral ear stimulation. Left and right hemisphere recordings were obtained during separate recording periods at least one day apart.

A permutation list of possible sound intensity sequences employing the 4 sound pressure levels (24 different sequences in all) was made and subjects were randomly assigned a sound sequence for each recording session. Since 12 subjects were studied for both contralateral and ipsilateral stimulation of both left and right hemisphere, the list was gone through twice. Each recording session (left or right hemisphere) was done in two trials: one for contralateral stimulation and one for ipsilateral stimulation, the order of which was varied randomly, but an attempt was made to specifically reverse the order from one session (left) to the other (right). A biological noise (no sound) control recording was made for both contralateral and ipsilateral trials. The resulting average waveforms were digitized and analyzed with respect to the following three dependent variables: (1) maximum peak to trough amplitude (P-T Amp) of the evoked response from the point of sound onset to a point 200 msec later; (2) total rectified area (Area) under the curve for the same interval; (3) latency highest amplitude response occurring in this time period, which generally (but not always) corresponded to the AEP N100 (L_{N100}) component and analogous AEF component. Additionally, waveforms for each sound intensity level (and the no sound control) were averaged across all 12 subjects for both hemispheres and both ipsilateral and contralateral ear stimulation, providing an overall average with a measure of variance. These average waveforms were analyzed in a manner similar to that described above. Independent variables included (1) sex (male or female), (2) hemisphere (left vs. right), (3) laterality (ipsilateral vs. contralateral ear stimulation, (4) stimulus intensity (0, 40, 60, 80 and 100 dB). A 2_b x 2w x2w x 5w x 6 (nested) multivariate ANOVA was carried out spearately for each dependent variable for both AEPs and AEFs. All waveforms from all subjects were included in the analysis of variance, which, in the case of poor responses, increased the variability.

Results

Good quality AEFs were the rule at all stimulus levels from 40 to 100 dB SPL. There was, of course, considerable individual variability, with some subjects demonstrating higher amplitude responses than others. In contrast, AEPs were more difficult to detect, especially at lower stimulus intensities, which is not surprising for temporal recording sites. For this reason, both amplitude and latencies to certain major components have been examined for AEFs, whereas for AEPs, response amplitude values are likely to provide more information than waveform latency values.

We have listed the statistically significant (p = .05 or better) ANOVA findings for the 3 dependent variables for both AEFs and AEPs in the six numbered frames of Table 1. The six frames of Table 1 will be discussed sequentially, in pairs, and illustrated where appropriate.

Frames 1 and 2 (dependent variable = maximum peak to trough amplitude during first 200 msec after stimulus onset).

The most prominent effect was an intensity main effect seen for both AEFs (F = 38.8, dF = 4/40, p < .0001) and AEPs (F = 38.9, dF = 4/40, p < .0001). AEF amplitude was related to stimulus intensity in a quadratic fashion (F = 93.2, dF = 1/40, p <.0001), rising steeply at first from 40 to 60 dB, peaking at 80 dB, and slightly declining at 100 dB. AEP response amplitude was related to stimulus intensity in a linear fashion (F= 50.3, dF = 1/40, p <.0001). The maximum peak-to-trough response amplitude vs. stimulus intensity functions for AEFs and AEPs are illustrated in Figure 1.

The AEFs also exhibited a laterality main effect. That is, contralateral responses were of larger amplitude than ipsilateral responses (F = 5.32, dF = 1/10, p <.05). AEPs did not exhibit such a relationship, but did however exhibit a laterality by sex interaction effect, in that males exhibited relatively larger contralateral responses, females relatively larger ipsilateral responses (F = 8.30, dF = 1/10, p <.02).

There was a significant hemisphere by intensity interaction effect for AEF amplitude, in that the right hemisphere responses were found to be larger than the left hemisphere responses, with maximal effect at 80 dB SPL (F = 4.19, dF = 4/40, p < .007). For AEPs we found a trend for males to exhibit a slightly larger left hemisphere response than right and for females to exhibit a greater right hemisphere response than left (F = 4.53, dF = 1/10, p < .06).

Frames 3 and 4 (dependent variable = total area under the curve in the first 200 msec)

Both AEFs and AEPs exhibited an intensity main effect. AEF areas increased with increasing stimulus intensity (F = 38.2, dF = 4/40, p < .0001), and the relationship was best described by a quadratic function. AEP areas also increased with increasing stimulus intensities (F = 35.2, dF = 4/40, p < .0001), but the relationship more closely approximated a linear one. These results are illustrated in Figure 2.

There was also evidence of a hemisphere by intensity interaction effect for AEFs. Right hemisphere responses were of larger area than left hemisphere responses. The effect varied at different sound intensities, maximally seen at 80 dB SPL (F = 4.16, dF = 4/40, p < .007). Such a relationship did not hold for AEPs.

Frames 5 and 6 (N100 latency)

AEFs exhibited an intensity main effect, with the MEG N100 analog latency decreasing with increasing stimulus intensity (F = 9.66, dF = 4/40, p < .0001). AEPs demonstrated a hemispheric main effect, with left hemisphere latencies being less, or shorter than, R hemisphere latencies (F = 8.58, dF = 1/10, p < .02)

Experiment 2

Methods

In Experiment 2, AEF and AEP recordings obtained from the above (Experiment 1) 12 subjects, for the right hemisphere contralateral ear stimulation condition, were combined with the same data, recorded using the same experimental conditions, collected from the 24 adult subjects reported in

Reite et al. (4). This combination provided a total of 36 subjects (3 used twice) with AEFs and AEPs recorded from the same right hemisphere location in response to 100 msec 1 KHz tone pips at 40, 60, 80 and 100 dB delivered to the contralateral (left) ear. An average AEF and AEP response was obtained from all 36 subjects at each stimulus intensity level, as well as a no sound control. The configuration and the latency of the earliest well defined component for both AEFs and AEPs was measured and compared as a function of stimulus intensity. We believe this component is that generally referred to as the P50 in the EEG evoked potential literature.

Results

The averaged AEF and AEP waveforms obtained from the 36 subjects used in Experiment 2 are illustrated in Figure 3. The waveform being identified as the AEP P50 or MEG P50 analog is marked with an arrow in each tracing. In actuality, the latency of this waveform ranges from a maximum of 82 msec in AEPs to 40 dB stimuli, to a minimum of 44 sec in AEFs to 100 dB stimuli. Being generally better defined in magnetic recordings, its latency decreases as a function of increasing stimulus intensity for both AEFs and AEPs. The relationship is essentially linear in both cases. Noteworthy, is the observation that AEF latency is consistently less than the AEP latency from the same area on the scalp for all sound intensities studied. The relationships are illustrated in Figure 4, when P50 latency for both AEFs and AEPs are plotted as a function of increasing stimulus intensity.

We also examined, in the group of 36 subjects, the relationship between AEF and AEP response amplitude (within the first 200 msec) and stimulus intensity. AEP amplitude was again found to increase linearly with stimulus intensity, whereas AEF amplitude was maximal at 80 dB SPL, and then decreased slightly at 100 dB SPL.

Discussion

The present findings replicate two earlier reports of AEF asymmetry (1,2) with magnetic field evoked by contralateral auditory stimulation being greater in magnitude than those evoked by ipsilateral stimulation. We also found, in the present study, that total rectified area under the response curve (a different measure of waveform amplitude) for both AEFs and AEPs exhibited a similar relationship. That is, total integrated response areas to contralateral stimulation were greater than integrated response areas following ipsilateral stimulation, a not unexpected finding. A similar relationship was also described in our recent study examining AEF and AEP response amplitude to tone, click, and white noise stimuli (3). Having thus been essentially independently replicated several times, the finding would appear robust. The most plausible explanatory mechanism lies in the fact that the majority of centripetal auditory input is crossed. We also found in the present study an AEP laterality by sex interaction, with males exhibiting larger contralateral responses, females larger ipsilateral responses. The significance of this relationship is not clear. The possibility of its being due to chance, (i.e., a Type 1 error), cannot be excluded.

This study replicated as well our previous findings as concerns response amplitude vs. stimulus intensity (5). For AEPs, the relationship is linear, for AEFs it appears quadratic, even decreasing at the highest stimulus intensity (100 dB SPL). In another study of magnetic response amplitude vs. stimulus intensity, Elberling et al. (2) found that, in the case of contralateral auditory stimulation, response amplitude tended to keep increasing with increasing stimulus intensity (up to 85 dB), whereas with ipsilateral ear stimulation response amplitude may have begun to decrease slightly at the stimulus highest intensity level. Simultaneously AEPs were not reported in that study.

It should be noted that there is a considerable literature relating EEG evoked potential amplitude to stimulus intensity. Most of these studies have utilized EEG recorded from the vertex, and while in general EEG response amplitude tends to increase with increasing stimulus intensity (6-9), there are important exceptions to this general rule. Buchsbaum and Pfefferbaum (10) found considerable individual differences in the response amplitude/stimulus intensity functions for vertex recorded AEPs to visual (flash) stimuli. While most subjects tended to demonstrate increasing amplitude with increasing stimulus intensity ("augmentors"), some subjects demonstrated a reduction in response amplitude at the highest stimulus intensity levels ("reducers"). Alterations in expected AEP response amplitude and stimulus intensity functions have also been described in some patients with mental disorders (11, 12). Clearly there are a number of areas that require further investigation utilizing different paradigms and subject populations with neuromagnetic recordings as the dependent variable.

The magnetic waveform that compares most closely in configuration and time course with the AEP P50, and which we termed the MEG P50 analog, showed a decrease in latency with increasing stimulus intensity very similar to that in the AEP. In both cases the latency/stimulus intensity function appeared to decrease in a linear fashion. The latency to the AEF component was consistently shorter than that of the AEP component, suggesting some dissociation between magnetic field (gradients) recorded with the MEG and the electric potentials recorded with the EEG to what seemingly should be a similar source. Examining Figure 3, this waveform appears to have a period of approximately 50 msec, which should not have been significantly attenuated or phase shifted by the bandpass filtering (2-40 Hz) used for EEG and MEG signals.

In a study of the scalp distribution of the auditory evoked potential, Picton et al. (13) suggested that the P50 (and later) waves may originate in frontal cortical regions. Subsequently, using magnetic recordings, Farrell et al. (14) were able to place the generator of the P50 as relatively deep within the auditory cortex. A recent mapping study from our laboratory (Zimmerman et al., unpublished data) clearly places the generator of the P50 analog in close proximity to the auditory cortex. The downward slope of the magnetic P50 analog illustrated in Figure 3 represents an upward pointing current dipole in the auditory cortical region.

The reason for the apparent dissociation between the AEF P50 and AEF P50 analog could be related to the fact that magnetic sensors are preferentially sensitive to tangential sources, where potential recordings are also sensitive to radial components. Thus as source geometry may vary with time, the same or similar sources may be resolved somewhat differently with the two detection techniques. Resolution of this question awaits further research.

Summary

Auditory evoked magnetic fields (AEFs) and EEG auditory evoked potentials (AEPs) were recorded from left and right auditory cortical regions of 12 normal adult subjects. The magnetic sensor was a figure-eight SQUID gradiometer with a 4 cm baseline oriented so as to be maximally sensitive to a current dipole oriented normal to the Sylvian fissure. Stimuli were 100 msec long 1 KHz tone pips with a modal interstimulus interval of 700 msec delivered at sound pressure levels of 40, 60, 80, and 100 dB. AEF amplitude was found to be related to stimulus intensity in a quadratic fashion, AEP amplitude in a

linear fashion. AEFs were of larger amplitude in response to contralateral as compared to ipsilateral stimulation. AEPs did not exhibit such a relationship.

In a second experiment right hemisphere AEFs and AEPs in response to contralateral ear stimulation tone in these 12 subjects were combined with similar previous data from 24 subjects, providing a total of 36 subjects, to examine the comparability of the AEP P50 waveform and the AEF P50 analog. The latency of the P50 was found to decrease as a function of increasing stimulus intensity for both AEFs and AEPs but the P50 latency was consistently shorter in magnetic compared to potential recordings.

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Figure Legends

Figure 1 Mean values for the highest amplitude AEFs (solid lines) and AEPs (broken lines) occurring during the first 200 msec for 12 subjects at each of four stimulus intensities and for a biological noise (no stimulus) control. Vertical brackets represent standard error of the mean.

Figure 2 Absolute value of integrated area for AEFs (solid line) and AEPs (broken lines) at four stimulus intensities and for a biological noise control (B) for the first 200 msec after the stimulus reaches the ear. Vertical brackets represent standard error of the mean.

Figure 3 Mean right hemisphere AEF and AEP average responses from 36 subjects at four stimulus intensities with a biological noise control average for comparison. Sound reached subject at the point indicated by the left most arrow in each trace. The component we have identified is the P50 analog is approximated by the second arrow in each tracing.

Figure 4 Latency in milliseconds for the P50 analog and AEF responses at four different stimulus intensities (solid lines) and to the P50 in AEP responses recorded from the same area to the same stimuli (broken lines).

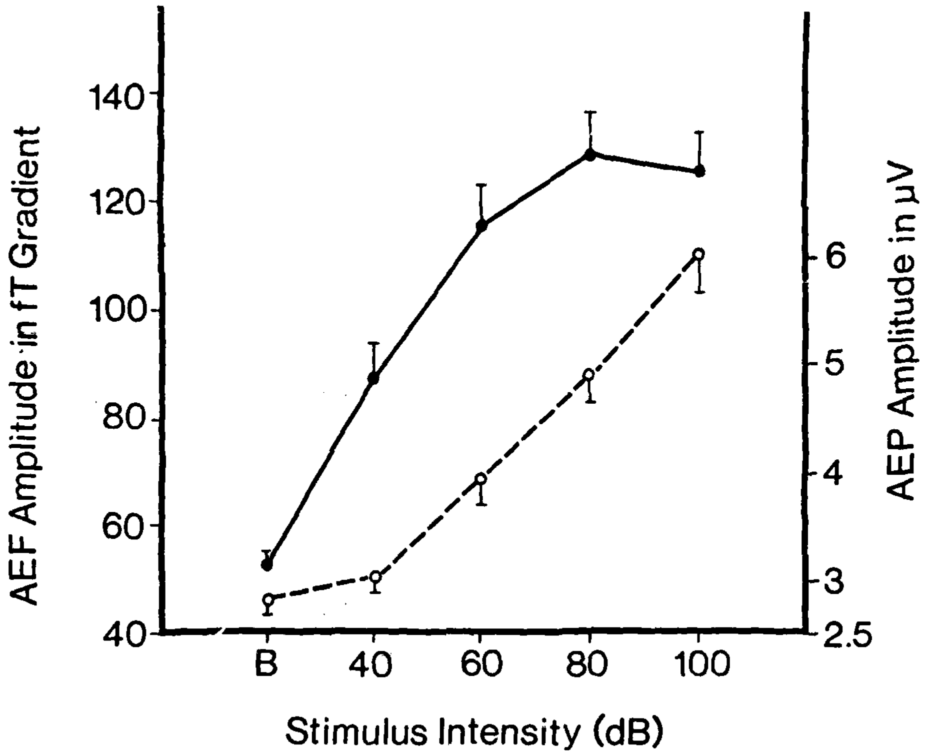

Figure 1

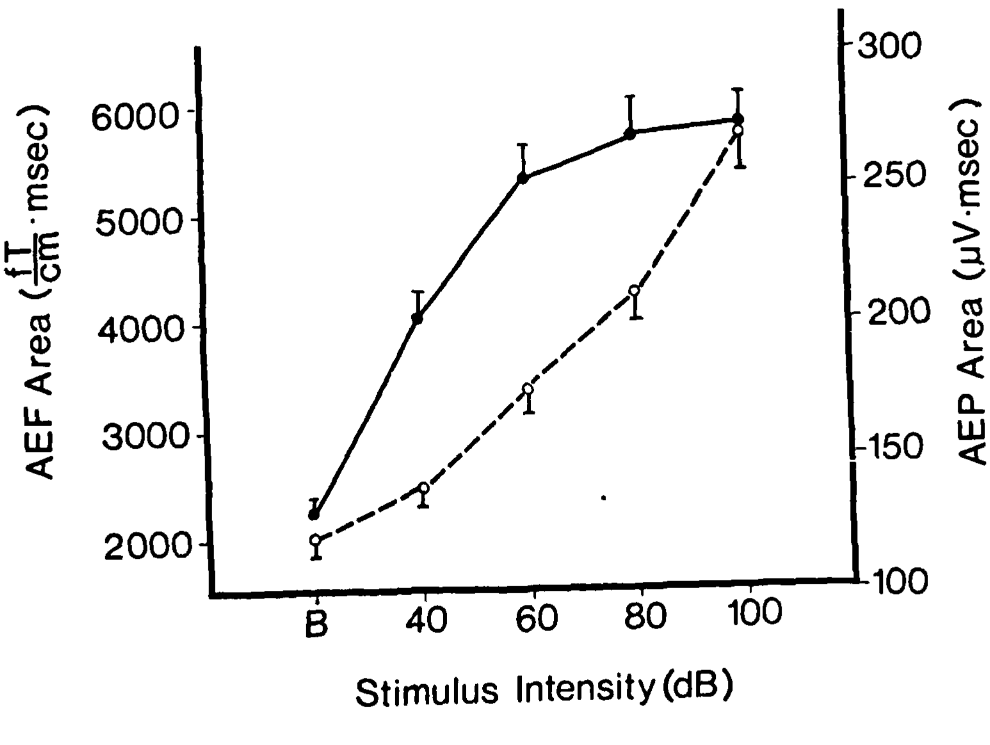

Figure 2

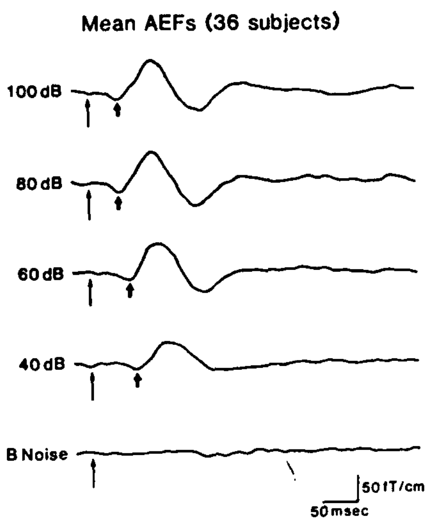

Figure 3

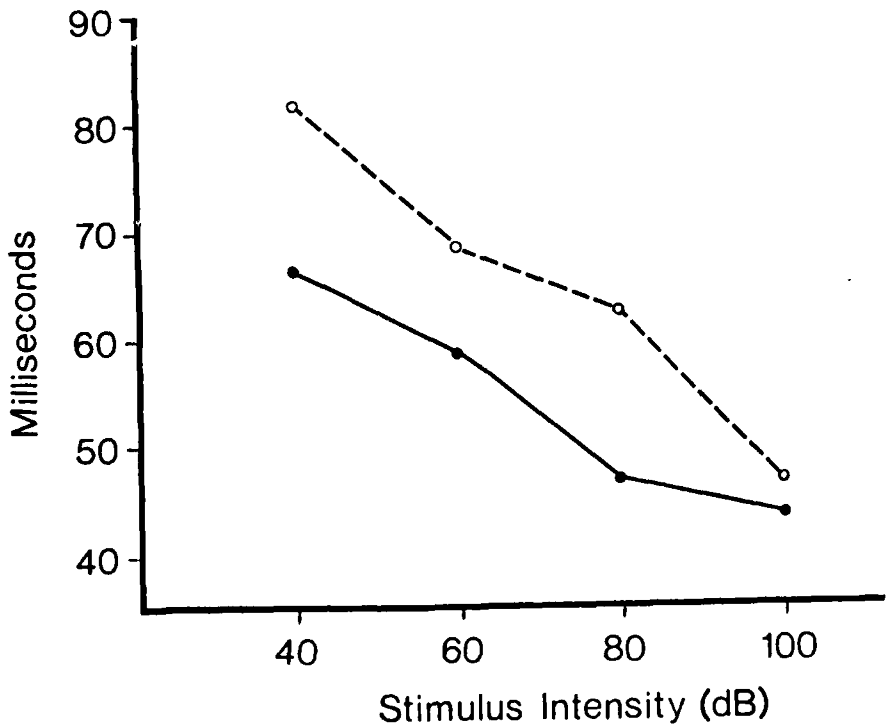

Figure 4

Variable	AEFs	AEPs
P-T Amp	Frame 1 1. Intensity main effect. Response amplitude increases with increased stimulus intensity, with suggestive quadratic relationship. 2. Laterality main effect. Contralateral responses larger than ipsilateral. 3. Hemisphere by intensity interaction effect. Non-significant trend for R hemisphere response to be larger than L, maximal at 80 dB.	Frame 2 1. Intensity main effect. Response amplitude increases with increasing stimulus intensity, with linear relationship. 2. Laterality by sex interaction effect. Males exhibited larger contralateral responses, females larger ipsilateral responses. 3. In males there was a larger L hemisphere response; in females, there was a larger R hemisphere than L hemisphere response.
AREA	Frame 3 1. Intensity main effect. Response area related to stimulus intensity in suggestive quadratic fashion. 2. Hemisphere by intensity interaction effect. R hemisphere responses tended to be larger than L hemisphere responses, with maximal differences at 80 dB SPL.	Frame 4 1. Intensity main effect. Response area related to stimulus intensity in linear fashion.
L_{N100}	Frame 5 1. Intensity main effect. Latency decreases with increasing stimulus intensity with a suggestive quadratic relationship.	Frame 6 1. Intensity main effect. Latency decreased as intensity increased in a linear fashion. 2. Hemisphere main effect. L hemisphere had shorter latencies than R hemisphere.

Table 1

Significant ANOVA findings for AEFs and AEPs for 3 variables: maximum peak-to-trough in the first 200 msec (P-T Amp), total rectified area under the curve in the first 200 msec (Area), and latency of the N100 component (L_{N100}).